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BOX PATENT APPLICATION

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Elan Pharmaceutical Research Corporation
1300 Gould Drive
Gainesville, GA 30504

November 19, 1999

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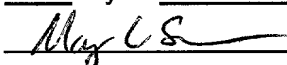
Transmitted herewith for filing are the specification and claims of the patent application of:

Inventor(s): **O'Mahony, Daniel Joseph and Seveso, Michela**

Title of Invention: **"ANTIBODIES TO PEPTIDES THAT TARGET GIT RECEPTORS
AND RELATED METHODS"**

Also enclosed are:

X	<u>5</u> Sheets of	<input checked="" type="checkbox"/> FORMAL DRAWINGS	<input type="checkbox"/> INFORMAL DRAWINGS
	OATH OR DECLARATION OF APPLICANT(S)		
	A POWER OF ATTORNEY		
	A PRELIMINARY AMENDMENT		
	A VERIFIED STATEMENT TO ESTABLISH SMALL ENTITY STATUS UNDER 37 C.F.R. §1.19 AND § 1.27		
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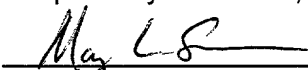
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Respectfully submitted,



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666777, 0364460

TO ALL WHOM IT MAY CONCERN:

Be it known that We, Daniel Joseph O'Mahony, a citizen of Ireland, residing at 75 Avoca Park, Avoca Avenue, Blackrock, County Dublin, Ireland, and Michela Seveso, a citizen of Italy, residing at Apartment 89, Marlborough Court, Marlborough Street, Dublin 1, Ireland, have invented new and useful improvements in

**Antibodies to peptides that target GIT
receptors and related methods**

for which the following is a specification.

Antibodies to peptides that target GIT receptors and related methods

FIELD OF THE INVENTION

5 The present invention relates to antibodies to random peptides capable of targeting or specifically binding to gastro-intestinal tract (GIT) transport receptors. In particular, this invention relates to methods of using these antibodies as well as specific antibody preparations directed to particular GIT random peptide targeting agents.

BACKGROUND OF THE INVENTION

10 Antibodies can be produced by using an immunogen to generate antibodies which immunospecifically bind such an immunogen. Such antibodies include but are not limited to polyclonal, monoclonal, chimeric, single chain, Fab fragments, and an Fab expression library.

15 Various procedures known in the art may be useful for the production of polyclonal antibodies to an immunogen. For the production of antibody, various host animals, such as rabbits, mice, rats, fowl etc. can be immunized by injection with the immunogen. Various adjuvants may be used to increase
20 the immunological response, depending on the host species, such as Freund's (complete and incomplete), mineral gels such as aluminum hydroxide, surface active substances such as lysolecithin, pluronic polyols, polyanions, peptides, oil emulsions, keyhole limpet hemocyanins, dinitrophenol, and potentially useful human adjuvants such as BCG (bacille
25 Calmette-Guerin) and corynebacterium parvum.

 As disclosed and claimed in WO 98/51325, which reference is hereby incorporated by reference in its entirety, we have identified random peptides and their fragments, motifs, derivatives, analogs or peptidomimetics thereof which are capable of specific binding to GIT transport receptors such as the

D2H, hSI, HPT1 and hPEPT1 receptors (hereinafter referred to as "GIT targeting agents"). These GIT targeting agents are capable of facilitating transport of an active agent through a human or animal gastro-intestinal tissue and have use, for example, in facilitating transport of active agents
5 from the luminal side of the GIT into the portal, hepatic or systemic blood system and/or in targeting active agents to the GIT. Thus, for example, by binding (covalently or noncovalently) the GIT targeting agent to an orally administered active agent, the active agent can be targeted to specific receptor sites or transport pathways which are known to operate in the human
10 gastrointestinal tract, thus facilitating its absorption into the systemic system. Preferably, the active agent is a drug or a drug-containing nano- or microparticle. Preferably, the tissue through which transport is facilitated is of the duodenum, jejunum, ileum, ascending colon, transverse colon, descending colon, or pelvic colon. The tissue is most preferably epithelial
15 cells lining the luminal side of the GIT.

The GIT targeting agents are bound to a material comprising an active agent. Such compositions have use in targeting the active agent to the GIT and/or in facilitating transfer through the lumen of the GIT into the systemic circulation. Where the active agent is an imaging agent, such compositions
20 can be administered *in vivo* to image the GIT (or particular transport receptors thereof). Other active agents include but are not limited to: any drug or antigen or any drug- or antigen-loaded or drug- or antigen-encapsulated nanoparticle, microparticle, liposome, or micellar formulation capable of eliciting a biological response in a human or animal. Examples of drug- or
25 antigen-loaded or drug- or antigen-encapsulated formulations include those in which the active agent is encapsulated or loaded into nano- or microparticles, such as biodegradable nano- or microparticles, and which have GIT targeting agents adsorbed, coated or covalently bound, such as directly linked or linked via a linking moiety, onto the surface of the nano- or microparticle.
30 Additionally, the GIT targeting agent can form the nano- or microparticle itself or the GIT targeting agent can be covalently attached to the polymer or

polymers used in the production of the biodegradable nano- or microparticles or drug-loaded or drug-encapsulated nano- or microparticles or the peptide can be directly conjugated to the active agent.

5 The GIT targeting agent bound to the active agent can be employed in methods of treatment (and prophylaxis) by administration to a subject of an effective amount of targeting agent/active agent. Any disease or disorder of interest amenable to therapy or prophylaxis by providing a drug *in vivo* systemically or by targeting a drug *in vivo* to the GIT (by linkage to a GIT targeting agent) can be treated or prevented by this administration. Any route
10 of administration known in the art may be used, including but not limited to oral, nasal, topical, intravenous, intraperitoneal, intradermal, mucosal, intrathecal, intramuscular, etc. Preferably, administration is oral.

However, to fully characterize the compositions as well as to determine the fate of the compositions following administration to a subject, antibodies
15 to the specific GIT targeting agents are needed.

SUMMARY OF THE INVENTION

The present invention provides antibodies or antibody fragments specific to a domain of a GIT targeting agent, particularly antibodies to ZElan033 (PAX2 15 mer), ZElan088(HAX42-2 20 mer) and ZElan053 (P31 D-
20 form 16 mer).

Additionally, numerous methods are provided below that employ the GIT targeting agent specific antibodies of this invention, including methods of detecting, quantitating, and locating the GIT targeting agent either in a pharmaceutical composition or after contact of a GIT targeting agent-
25 containing composition with human or animal gastro-intestinal tissue.

BRIEF DESCRIPTION OF THE DRAWINGS

Figure 1 shows the immuno responses of three groups of 2 rabbits, each group immunized, respectively, with one of KLH conjugated ZElan033, KLH conjugated ZElan088 and KLH conjugated ZElan053, when the fourth bleed samples are tested by ELISA on their respective unconjugated peptides;

Figure 2 shows the crossreactivity of rabbit antisera for three groups of 2 rabbits, each group immunized, respectively, with one of KLH conjugated ZElan033, KLH conjugated ZElan088 and KLH conjugated ZElan053, when the fourth bleed samples are tested by ELISA on each of synthetic peptides HAX42.2, PAX2 15 mer and P31-D-form;

Figure 3 shows the immuno-reactivity of anti-HAX42-2 antisera (fifth bleed samples) on a variety of synthetic peptides;

Figure 4 shows the immuno-reactivity of anti-PAX2 antisera (fifth bleed samples) on a variety of synthetic peptides; and

Figure 5 shows the immuno-reactivity of anti-P31 D-form antisera (fifth bleed samples) on a variety of synthetic peptides.

DETAILED DESCRIPTION OF THE INVENTION

According to this invention, a GIT targeting agent may be used as an immunogen to generate antibodies which immunospecifically bind such an immunogen. Such antibodies include but are not limited to polyclonal, monoclonal, chimeric, single chain, Fab fragments, and a Fab expression library. Particular antibodies provided by this invention include but are not limited to antibodies or antibody fragments, preferably polyclonal antibodies or antibody fragments, specific to a domain of GIT targeting agents ZElan033 (PAX2 15 mer), ZElan088 (HAX42-2 20 mer) and ZElan053 (P31 D-form 16

mer). Additional GIT targeting agents are disclosed throughout the above-referenced WO 98/51325.

These antibodies can be used in methods relating to the localization and activity of the GIT targeting agent sequences, e.g., for imaging these peptides after *in vivo* administration (e.g., to monitor treatment efficacy), measuring levels thereof in appropriate physiological samples, in diagnostic methods, etc. For instance, antibodies or antibody fragments specific to a domain of a GIT targeting agent, such as a dansyl group or some other epitope introduced into the peptide, can be used to

- 1) identify the presence of the peptide on a nanoparticle or other substrate;
- 2) quantify the amount of peptide on the nanoparticle;
- 3) measure the level of the peptide in appropriate physiological samples;
- 4) perform immunohistology on tissue samples;
- 5) image the peptide after *in vivo* administration;
- 6) purify the peptide from a mixture using an immunoaffinity column;
- 7) bind or fix the peptide to the surface of nanoparticle or
- 8) when a tag is also added to either an active-agent containing particle or the active agent itself, track the fate of both the particle/active agent and the GIT targeting agent so as to determine if and/or where they become separated.

Use 7 above envisions attaching the antibody (or fragment of the antibody) to the surface of drug-loaded nanoparticles or other substrates and then incubating this conjugate with the peptide. This procedure results in binding of the peptide in a certain fixed orientation, resulting in a particle that contains the peptide bound to the antibody in such a way that the peptide is fully active. Additionally, antibodies or antibody fragments specific to a domain of a GIT targeting agent

- 9) can be used in confocal microscopy imaging techniques or other imaging techniques in order to demonstrate or confirm or identify the location or localization of the peptide on the surface of a nano- or microparticle;
- 10) can be used in confocal microscopy imaging techniques or other imaging techniques in order to demonstrate or confirm or identify the location or localization of the peptide on the surface of a nanoparticle or microparticle which has also been loaded with a fluorescent agent;
- 11) in the case of nanoparticles or microparticles coated

with the peptide which have been sliced into two halves by a microtone or other suitable techniques, the antibody can be used in suitable quantitative techniques such as confocal microscopy imaging techniques or other quantitative imaging techniques in order to identify or quantitate the relative distribution of the peptide between the surface of the nanoparticle or microparticle and the sub-surface interior matrix of the nanoparticles or microparticles, 12) can be used in confocal microscopy imaging techniques or other imaging techniques in order to demonstrate or confirm or identify the location of a peptide on the surface of a nanoparticle or microparticle which has been loaded with a fluorescent agent such as TRME or fluorascene, 13) can be used to identify which epitope or domain of the peptide is responsible for identification by the antibody; peptide derivatives such as cyclic forms or derivatives containing intra-chain disulphide bonds or other intra-chain bonds can also be used in mapping studies in order to identify which domain or epitope of the peptide is responsible for recognition by the antibody; 14) in the case of peptide derivatives in which the epitope or domain responsible for binding to a target receptor is flanked by di-sulphide bond or other intra-chain bonds and in which this domain is also responsible for binding to the antibody, the antibody can be used to determine if that epitope or domain is exposed or available for binding to the antibody when the peptide or derivative is coated onto the surface of a nanoparticle, microparticle or other substance, 15) can be used where the epitope or domain on the peptide which binds to the target receptors in the human gastro-intestinal tract or the target receptors on model epithelial cells such as Caco-2 cells or polarised Caco-2 cells and where this epitope or domain on the peptide is also responsible for binding by the antibody, the antibody can be used in competition studies to compete for the binding of the peptide to its target receptor sites and 16) where the epitope or domain on the peptide which binds to the target receptors in the human gastro-intestinal or the target receptors on model epithelial cells such as Caco-2 cells or polarised Caco-2 cells and where this epitope or domain on the peptide is also responsible for

binding by the antibody, the antibody can be used in competition studies in which nanoparticles or microparticles are coated with the peptide and are used in cell binding studies and / or in receptor binding studies.

Polyclonal antibodies against the GIT targeting agents PAX2 15mer, HAX42-2 20mer and P31D-form 16mer were raised to allow for, among other uses as discussed above, following the destiny of particles coated with peptides in *in vivo* models. These three GIT targeting agents were selected for their ability to bind *in vitro* to Caco-2 P100 fraction and, when coated on the surface of insulin loaded nanoparticles, to enhance insulin delivery in *in vivo* studies (rat model/intra-duodenal). The primary sequences for these three GIT targeting agents are given in Table 1.

Table 1		
NAME	SEQUENCE	N° OF AMINO ACIDS
ZELAN033	K(dns)-TNAKHSSHNRRRLRTR	PAX2 15 mer
ZELAN088	K(dns)-SDNAKEPGDYNCCGNGNSTG	HAX42-2 20 mer
ZELAN053	K(dns)-TrKSSrSNPrGrrHPG	P31 D form 16 mer

The amino acids indicated in lower case and in bold are D-amino acids; K(dns) refers to a dansyl group

The peptides were synthesised (Genosys) and conjugated to KLH protein in preparation to immunise rabbits. KLH protein was conjugated at both N- and C- terminals in order to maximise the probability of obtaining specific antibodies.

The immunization protocol provided that two rabbits were immunized for each peptide; Rabbits 122 and 123 were immunized with PAX215 mer, Rabbits 120 and 121 were immunized with HAX42-2 20 mer and Rabbits 141 and 142 were immunized with P31 D-form 16mer. The initial immunisation was given in Complete Freund's adjuvant and the remaining boosts in Incomplete Friends. A pre-immune sample was taken from each animal

before immunization. The rabbits were injected at day 0, day 14 and 28, bled a week later at day 35 (1st bleed), boosted a week later at day 42 and bled a week later at day 49; this sequence of injections and bleeds was performed every two weeks.

5 The bleed samples were tested by ELISA using the following procedures: 96 well plates were coated with peptide at 50 µg/ml in 0.05M carbonate/bicarbonate buffer, pH9.6, overnight. The plates were washed twice with PBS + 0.05% Tween20 and the plates were blocked with 2% dried skimmed milk (99% fat free) in PBS for one hour at room temperature. The
10 plates were then washed three times with PBS + 0.05% Tween20 and anti-sera diluted in 2% dried milk-PBS was added followed by incubation for one hour at room temperature. The plates were then washed three times with PBS + 0.05% Tween20 and secondary antibody goat anti-rabbit IgG-HRP (Sigma A0545, dilution 1:20000) in 2% dried milk-PBS was added followed by
15 incubation for one hour at room temperature. The plates were washed three times with PBS + 0.05% Tween20, TMB substrate was added, incubated and the absorbance was read at 650nm.

 The fourth bleed samples were tested by ELISA on both the peptides used for immunisation (but not conjugated to KLH) and on different
20 (dansylated) peptide batches. Pre-immune serum was included in the assay as negative control and background binding to plastic was also tested. As shown in Figure 1, the antisera of the immunised rabbits gave an antibody response compared to pre-immune sera of the same animals. The immuno response of the two rabbits immunised in each protocol was comparable
25 except that Rabbit 120 showed a lower antibody titer with respect to Rabbit 121. Crossreactivity of each rabbit antiserum on different peptides was also analysed by ELISA as shown in Figure 2 and no significant cross-reactivity was detected.

 The fifth bleed samples were tested by ELISA as described above and
30 examples of the profiles obtained are shown in Figures 3, 4 and 5. A higher

titer of antibody was detected for each rabbit after this longer immunisation period compared to the fourth bleed results.

Figure 3 shows the immuno-reaction of anti-HAX42 antisera on synthetic peptides (sequences reported in the Figure). Panel A shows the ELISA results for rabbit #120 antisera: good immuno-response is obtained on unconjugated peptide used as antigen but no response was obtained for the same peptide conjugated to a dansyl group (Zelan088). No immuno-response is observed for the other peptides analysed. Panel B shows the ELISA results for rabbit #121 antisera: in this case there also was good immuno-response for the unconjugated peptide used as antigen but no response for Zelan088 dansyl-peptide. Rabbit #121 antisera is positive (although less strongly) against Zelan021 (HAX42) and Zelan071 (HAX42 29mer derivative). Panel C shows the response of anti-dansyl IgG on the peptides used in the assay.

Figure 4 shows the immuno-reactivity of anti-PAX2 antisera on synthetic peptides. Rabbit #122 (panel A) and #123 (panel B) have a different immuno-response. Both antisera react in the same way to the unconjugated peptide (=Zelan033) used for immunisation. Rabbit #123 antisera has also very strong reactivity against Zelan103A peptide whereas rabbit #122 does not bind to the same peptide. Rabbit #123 antisera has also immuno-response against both Zelan104 and Zelan018. Panel C shows the response of anti-dansyl IgG on the peptides used in the assay.

Figure 5 shows the immuno-reactivity of anti-P31 D-form antisera on synthetic peptides. Both rabbit #141 and #142 react equally well on P31 D-form unconjugated peptide (=Zelan053). No reactivity is present against all the other peptides tested.

Table 2 provides a summary of the fifth bleed results.

Table 2					
Rabbit Number		Peptides			
		<i>Zelan021</i>	<i>Zelan071</i>	<i>Zelan088</i>	<i>Unconjg. antigen (=Zelan088)</i>
(HAX42)	Rabbit 120	-	-	-	+
	Rabbit 121	+	+/-	-/+	++
		<i>Zelan018</i>	<i>Zelan104</i>	<i>Unconjg. antigen (=Zelan033)</i>	<i>Zelan103A</i>
(PAX2)	Rabbit 122	-/+	-/+	+	-
	Rabbit 123	+	+	+	++
		<i>Zelan024</i>	<i>Unconjg. antigen (=Zelan053)</i>	<i>Zelan054</i>	<i>Zelan145</i>
(P31 d-form)	Rabbit 141	-	+	-	-
	Rabbit 142	-	+	-	-

The present invention is not to be limited in scope by the specific embodiments described herein. Indeed, various modifications of the invention in addition to those described herein will become apparent to those skilled in the art from the foregoing description and accompanying figures. Such modifications are intended to fall within the scope of the appended claims.

CLAIMS

What is claimed is:

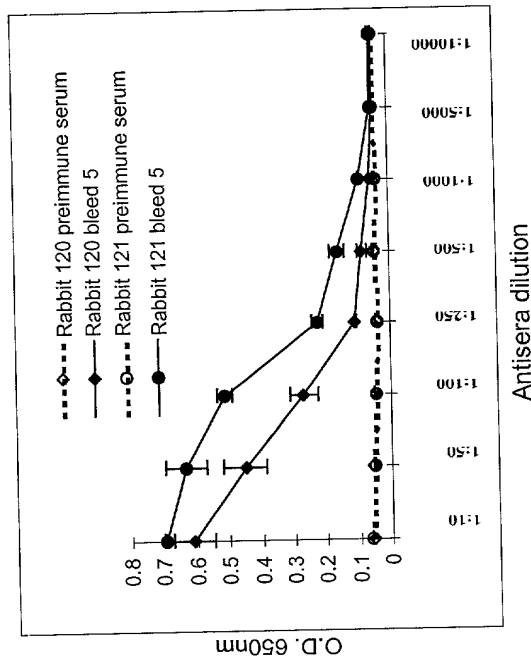
1. An antibody or antibody fragment specific to a domain of a GIT targeting agent.
2. The antibody or antibody fragment of claim 1, wherein the antibody or antibody fragment is selected from the group consisting of a polyclonal antibody, monoclonal antibody, chimeric antibody, single chain antibody, a Fab fragment or a Fab expression library.
3. The antibody or antibody fragment of claim 1, wherein the GIT targeting agent is selected from the group consisting of ZElan033 (PAX2 15 mer), ZElan088 (HAX42-2 20 mer) or ZElan053 (P31 D-form 16 mer).
4. A method of making an antibody or antibody fragment of claim 1, comprising the steps of (a) contacting a GIT targeting agent with the immune system of an animal under conditions conducive to formation of antibodies in a body fluid of the animal and (b) recovering the antibody or antibody fragment from the body fluid of the animal.
5. A method of identifying the presence of a GIT targeting agent in a composition or quantitating the amount of a GIT targeting agent in a composition, wherein the composition comprises the GIT targeting agent bound to an active agent, comprising the steps of (a) contacting an antibody or an antibody fragment specific to a domain of the GIT targeting agent with the composition under conditions conducive to binding between the antibody or antibody fragment and the GIT targeting agent; and (b) detecting the amount of antibody or antibody fragment that specifically binds to the GIT targeting agent.

6. A method of identifying the location of a GIT targeting agent in a composition, wherein the composition comprises the GIT targeting agent bound to an active agent, comprising the steps of (a) contacting an antibody or an antibody fragment specific to a domain of the GIT targeting agent with the composition under conditions conducive to binding between the antibody or antibody fragment and the GIT targeting agent; and (b) visualizing the position of the antibody or antibody fragment that specifically binds to the GIT targeting agent.
7. The method of Claim 6, wherein the composition comprises an active agent loaded nano- or microparticle bound to the GIT targeting agent.
8. A method of identifying the location of a GIT targeting agent following contact of a GIT targeting agent-containing composition with human or animal gastro-intestinal tissue, comprising the steps of (a) contacting an antibody or an antibody fragment specific to a domain of the GIT targeting agent with the composition under conditions conducive to binding between the antibody or antibody fragment and the GIT targeting agent; and (b) detecting the location of the antibody or antibody fragment that specifically binds to the GIT targeting agent.

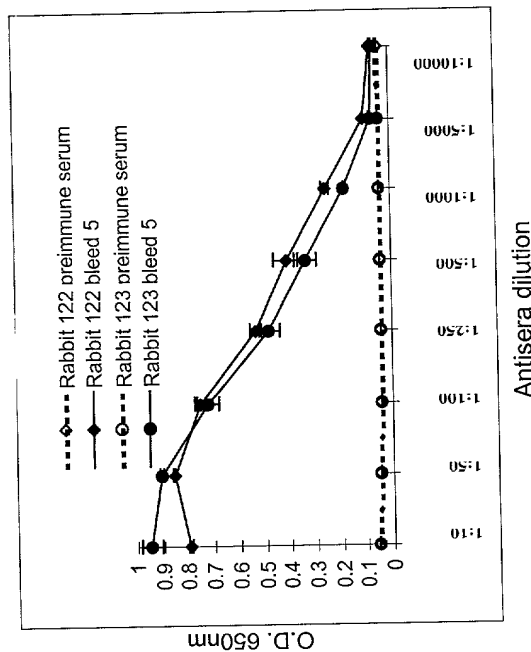
ABSTRACT

The invention provides an antibody or antibody fragment specific to a domain of a GIT targeting agent, such as a polyclonal antibody, monoclonal antibody, chimeric antibody, single chain antibody, a Fab fragment or a Fab expression library. In particular, the invention provides an antibody or antibody fragment, wherein the GIT targeting agent is selected from the group consisting of ZElan033 (PAX2 15 mer), ZElan088 (HAX42-2 20 mer) or ZElan053 (P31 D-form 16 mer). Numerous methods using these GIT targeting agent specific antibodies are disclosed.

Rabbit 120 and 121 antisera onto HAX42-2 antigen (RA2359, bleed 28/07/98)



Rabbit 122 and 123 antisera onto PAX2 15mer antigen (RA2358, bleed 28/07/98)



Rabbit 141 and 142 antisera onto P31-Dform antigen (RA2365, bleed 18/08/98)

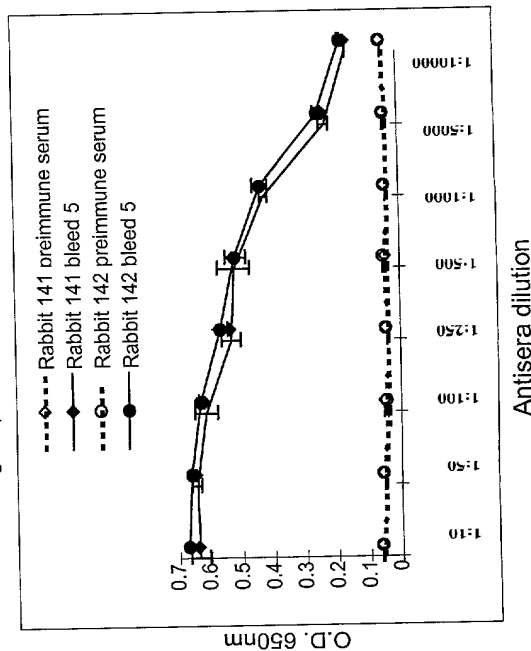


Fig. 1

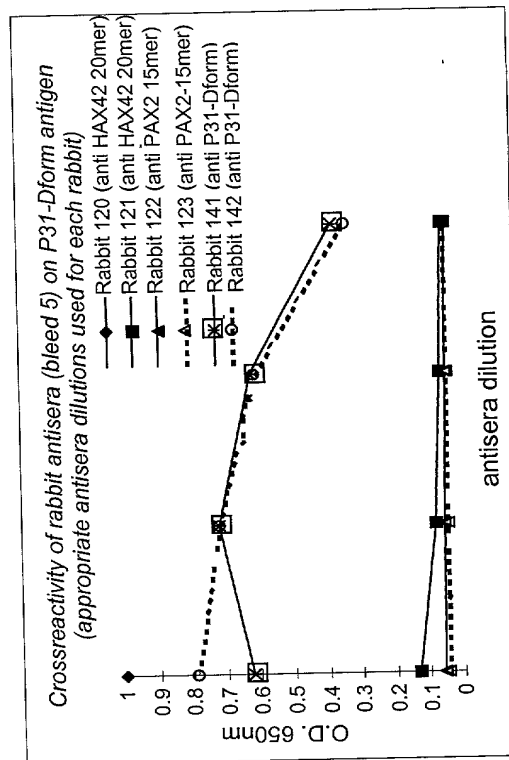
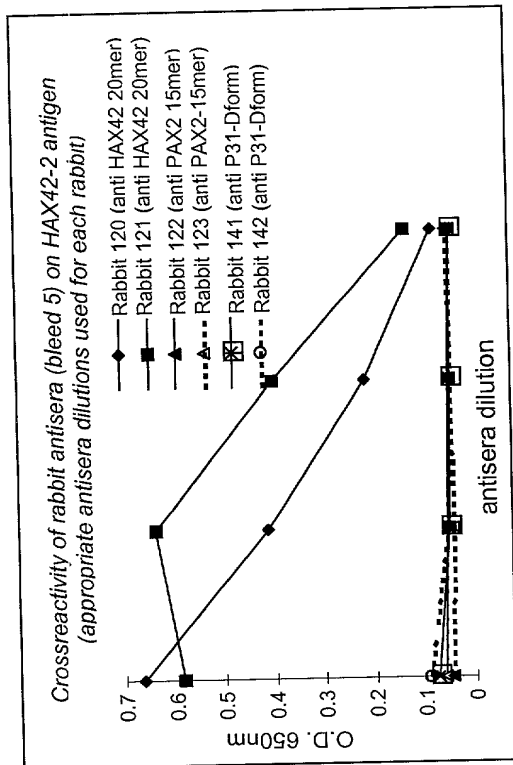
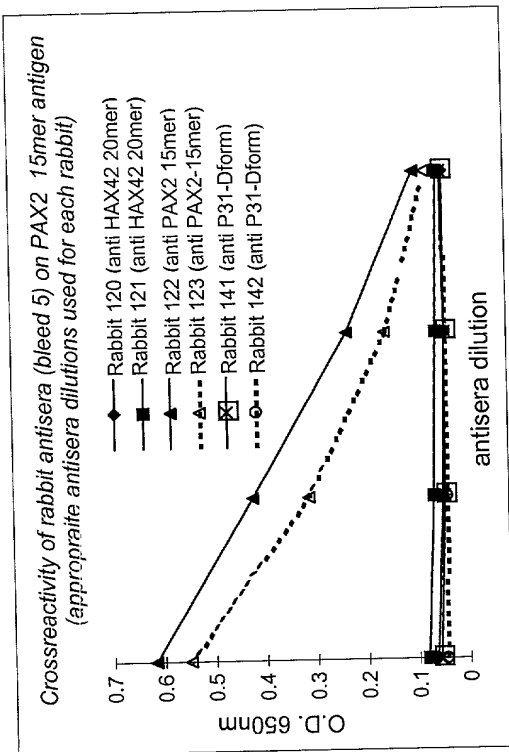
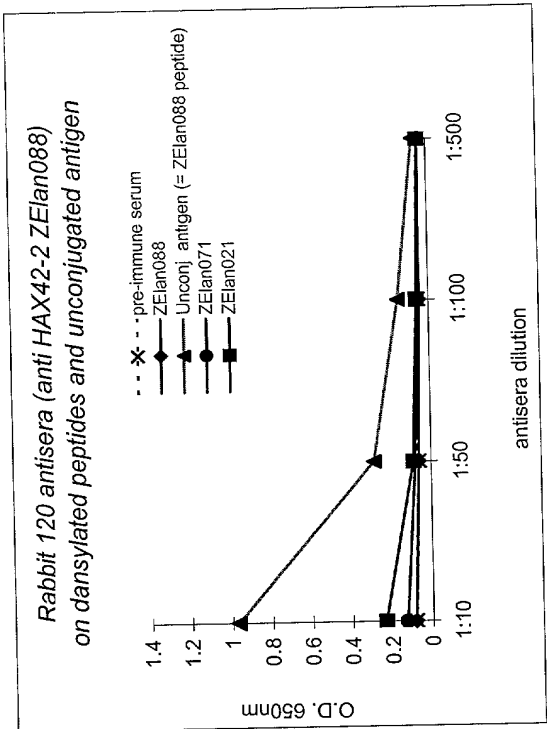
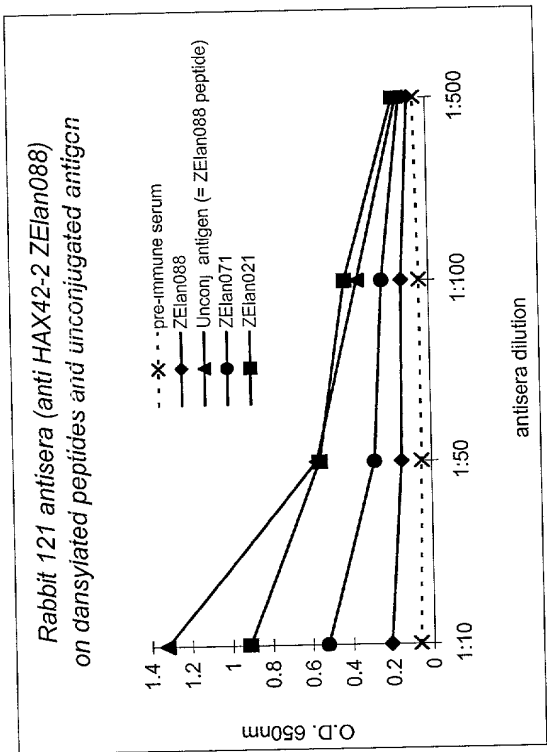


Fig. 2

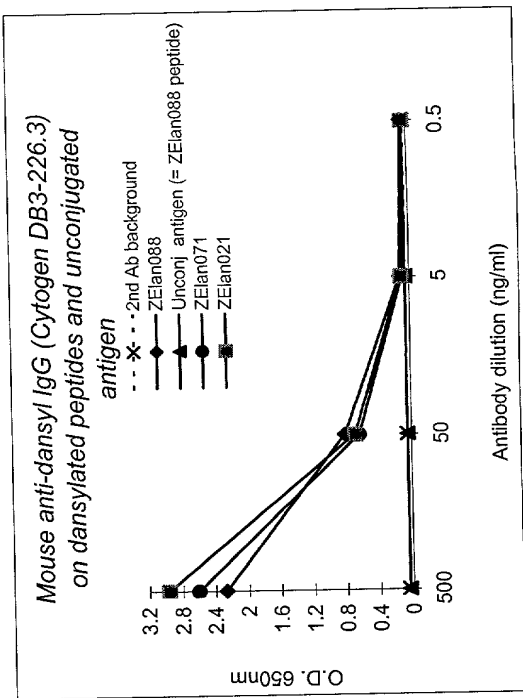
A



B

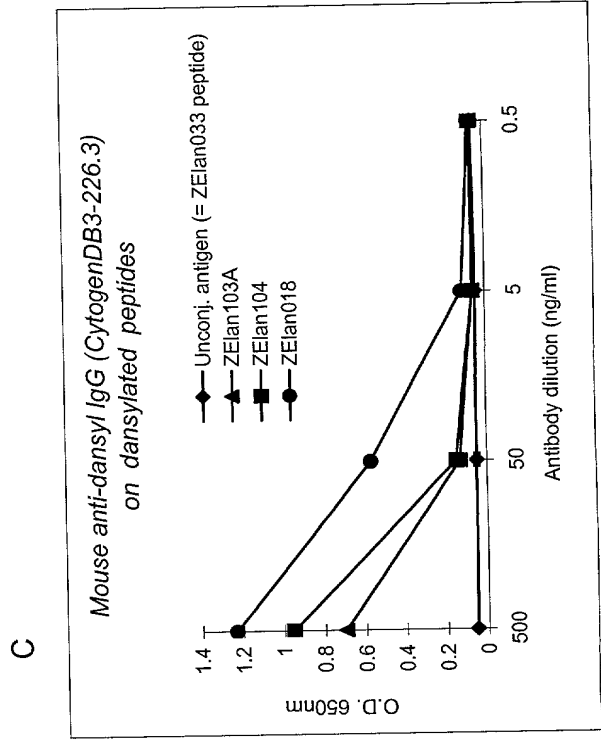
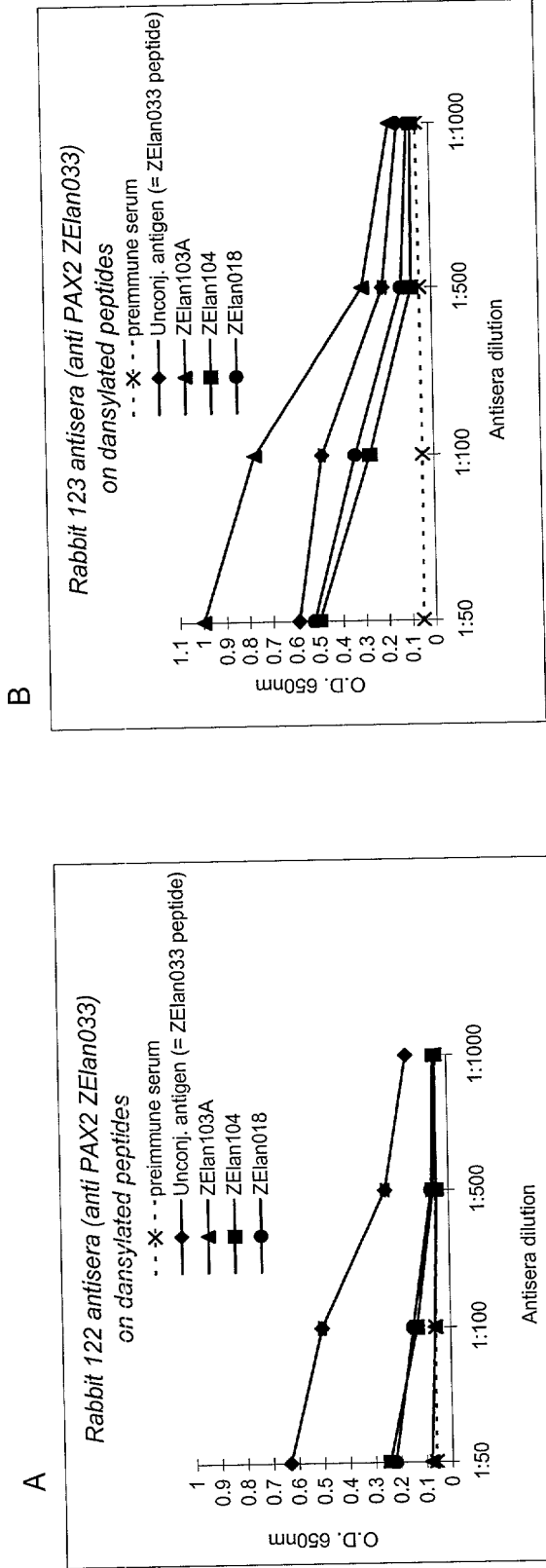


C



peptide	Description	Sequence
ZElan021	HAX42	SDHALGTNLRSDNAKEPGDYNCNGNGNSTGRKVENR
ZElan071	HAX42 (29mer)	NLRSDNAKEPGDYNCNGNGNSTGRKVENR
ZElan088	HAX42-2 (20mer)	SDNAKEPGDYNCNGNGNSTG
Unconjug. Antigen	HAX42-2 (20mer) no dansyl group	SDNAKEPGDYNCNGNGNSTG

Fig. 3



peptide	Description	Sequence
ZElan018	PAX2	STPPSREAYSRPYSVDSDTNAKHSSHNRLRTRSRPNG
ZElan104	PAX2 15mer cyclic (internal)	TNAKHSSCNRRLLRCR
Unconj. Ag	PAX2 15mer (= ZElan033)	TNAKHSSHNRLRTR
ZElan103A	PAX2 15mer cyclic (internal)	TNAKHSSCNRRCRTR

Fig. 4

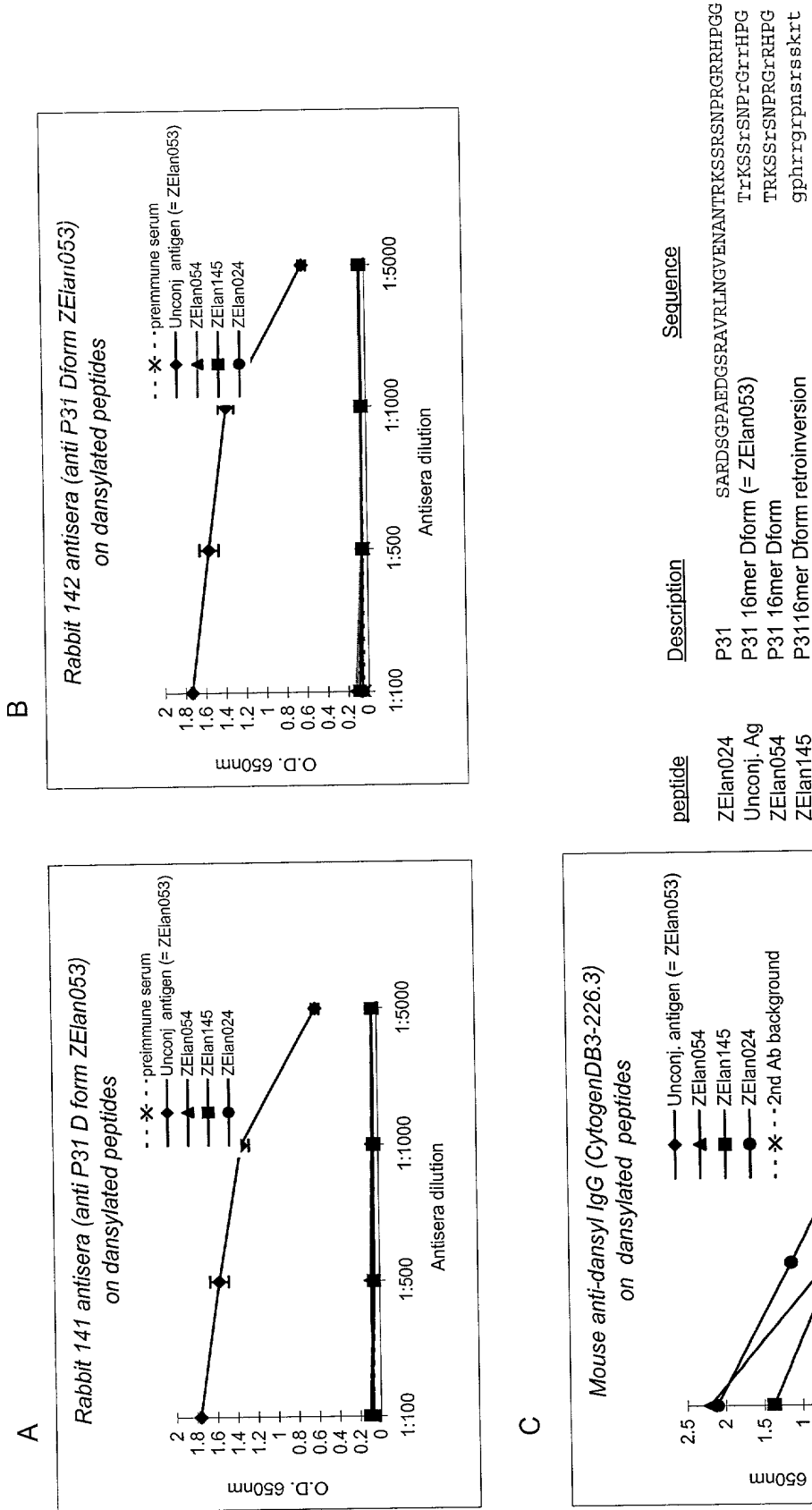


Fig. 5